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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,074	03/26/1999	LINDA A. SHERMAN	TSRI433.1DIV	3068

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/277,074	SHERMAN, LINDA A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/21/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 61-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1 and 61-71* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/30/04 has been entered.

Applicant adds new claims 61-71, which are related to claim 1 and are not new matter.

Accordingly, claims 1, 61-71 are examined in the instant application.

The following are the remaining rejections.

OBJECTION

Claims 64-67 are objected to, for the language "a second" component. It is not clear what is the first component.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claim 1 pertaining to lack of enablement for a method of specifically activating cytotoxic T lymphocytes *in vivo* in a patient having a tumor expressing HER-2/Neu, wherein said cytotoxic T lymphocytes

could target or kill tumor cells expressing HER-2/Neu *in vivo* in said patient remains for reasons already of record in paper No.24 of 06/18/03.

New claims 61-71 are rejected for the same reasons of record.

Applicant argues that the Examiner has misconstrued the test of enablement by requiring a working example that demonstrates a result that immunizing an animal with the claimed polypeptide of SEQ ID NO:10 results in the targeting or killing of tumor cells expressing Her-2/Neu in vivo, and that there is no requirement by law that a working example must be provided in the specification.

(1) The Breadth of the Claims and Nature of the Invention

Applicant argues that the claims, as amended, are limited to a method of activating CTLS in vïvo, wherein the CTLS specifically target malignant cells express a Her-2/Neu protein in vivo, comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10. Applicant argues that thus, the claimed invention requires immunization with a polypeptide which is fully disclosed in the specification including a disclosure of its sequence (SEQ IDNO:10). Applicant argues that the specification further discloses working example of the step of immunizing an animal with the polypeptide of SEQ ID NO:10 (see, page lines 25-30 which references, page 79, lines 7-12).

The arguments are deemed not to be persuasive. The scope of the claims is overly broad, encompassing a method for specifically activating cytotoxic T lymphocytes in **cancer patients with tumor burden, and having Her-2/ Neu as self-antigen in normal tissues, wherein said CTLs specifically kill target malignant cells that**

express a Her-2/Neu protein of said patients, comprising administering the peptide of SEQ ID NO:10.

The specification however only discloses activating cytotoxic T lymphocytes in transgenic mouse that is cancer free, and that does not express Her-2/Neu as self antigen in normal tissues. Further, the specification only discloses that said cytotoxic T lymphocytes could kill cancer cells line expressing Her-2/Neu in vitro.

2) The State of the Art and the Level of Skill in the Art

Applicant argues that the step of immunizing an animal with a polypeptide was routine in the art.

The Examiner takes note that although the step of immunizing a peptide is routine in the art, it is not known in the art that the specific peptide of SEQ ID NO:10 from Her-2/Neu protein could specifically activate cytotoxic T lymphocytes in cancer patients with tumor burden, and having Her-2/ Neu as self-antigen in normal tissues, wherein said CTLs specifically kill target malignant cells that express a Her-2/Neu protein of said patients.

3) The level of predictability in the Art

Applicant argues that Sherman et al does not teach that self-tolerance will occur for every peptide used as immugens. Applicant argues that self-tolerance does not eliminate the CTL response for all immunogens expressed at low levels by normal tissues as evidenced by Sherman et al.

Applicant further argues that Sherman et al (p.47, column 2, lines 4-16) teach that Her-1/neu is expressed at low levels in normal tissue of A2.1/K^b transgenic mice.

Applicant asserts that the present specification teaches that immunization of A2.1/K^b transgenic mice with SEQ ID NO:10 specifically activates CTLs in vivo, wherein these CTLs isolated from the immunized mice specifically target malignant cells that express the Her-2/Neu protein in vitro. Applicant asserts that thus self-tolerance does not eliminate the activated CTLs response to the immunogen SEQ ID NO:10 in vivo.

Concerning the Examiner assertion that it is unpredictable that mice having tumors that express Her/Neu would produce CTLs specific for SEQ ID NO:10 with high affinity, Applicant asserts that the claims do not recite the asserted element.

Applicant asserts that the tumor cell lines used for cell killing assays are a suitable model system for the correlation of in vitro results to in vivo conditions.

Concerning the Examiner assertion that the expression of Her-2/Neu could be lost in a tumor, due to autochthonous immune response, Applicant asserts that the Examiner fails to provide evidence that autochthonous immune response does occur, or that the response occurs in all individuals and tumors. Applicant asserts that further, the invention is not directed to cells that do not express a Her-2/Neu protein.

Concerning the Examiner assertion that in vitro, tumor cells are continuously exposed to CTLs and cytokines, which is not the case in vivo, Applicant asserts that the Examiner never provides evidence that this alleged difference of continuous exposure to CTLS and cytokines renders the in vitro targeting of malignant,cells that express a Her-2/Neu protein an irrelevant model system, or working example, for the targeting of malignant cells that express a Her-2/Neu protein in vivo. Applicant argues that for example, the Examiner never provides evidence that tumor cells in vivo are not also

continuously exposed to CTLS and cytokines after immunization with the polypeptide of SEQ ID NO:10.

Concerning the Examiner assertion that even if activated CTLS are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, Applicant argues that the claimed invention, as amended, is directed to those tumors that do express Her-2/Neu protein in vivo.

Applicant's arguments set forth in paper of 06/21/04 have been considered but are not deemed to be persuasive for the following reasons:

The level of unpredictability is very high in the instant application, due to:

1) the unpredictability of self-tolerance resulting in T cells with low affinity, as taught by Sherman et al, of record, and thus consequently the ability of the T cells to kill target malignant cells,

2) the well known immune tolerance and suppression phenomena in cancer as taught by Boon et al, of record, resulting in T cell anergy, and as disclosed in the specification (p.101),

3) the unpredictability of sufficient numbers of Her-2/neu molecules on cancer cells surface in patients, necessary for recognition and killing by T cells, due to antigen downregulation, as taught by Cheever et al, of record, or due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, of record, and

4) Non-correlation between in vitro killing of cancer cell lines expressing Her-2/Neu and with the in vivo killing of malignant cells by specific T cells, because the expression of antigens of cancer cells in culture cannot not be compared with those of primary cancer cells, due to cell culture artifact, based on the teaching of Freshney (of record) Dermer (of record), Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25), Embleton et al (Immunol Ser, 1984, 23:181-207), and Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764), and because in vitro assay cannot be correlated with in vivo conditions.

5) The unpredictability of tumor vaccination and anticancer drug discovery, as overwhelmingly evidenced by Ezzell et al, Spitler et al, Boon et al, Gurà et al, Jain et al, Curti et al, and Hartwell et al (of record).

More specifically, contrary to Applicant assertion, since Sherman et al teach that self-tolerance vary for different epitopes, one cannot predict that the particular SEQ ID NO:10 epitope of the Her-2/neu protein of the claimed invention would not elicit self-tolerance.

Further, Sherman on page 47, column 2, lines 4-16 do not teach that Her-1/neu is expressed at low levels in normal tissue of A2.1/K^b transgenic mice. On page 47, column 2, lines 4-16 Sherman actually teach that p53 and Her-2/neu are upregulated in a broad range of tumors, but are normally expressed self proteins. Thus there is no evidence that the transgenic mouse of the claimed invention expresses Her-2/neu as self protein. However, self tolerance could result in elimination of T cells with high

affinity for the target peptide, resulting in production of only low affinity T cells, as taught by Sherman et al.

Concerning Applicant assertion that the claims do not recite the asserted element, i.e. CTLs specific for SEQ ID NO:10 with high affinity, it is noted that although the claims do not specifically recite that the CTLs specific for SEQ ID NO:10 have high affinity, however, one could not predict that T cells with low affinity would have the ability to specifically target and successfully kill malignant cells in vivo.

Concerning Applicant's assertion that the tumor cell lines used for cell killing assays are a suitable model system for the correlation of in vitro results to in vivo conditions, this assertion is not supported by any references. On the contrary, the art teach that due to culture artifact, the expression of antigens of cancer cell lines could not be compared with those of primary cancer cells, due to cell culture artifact (Freshney and Dermer, of record). Similarly, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach

that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

Further, in vivo and in vitro conditions are different, such as continuous exposure to CTLs and cytokines in in vitro assay, which is not the case in vivo. It is noted that adequate exposure of CTLs and cytokines to the target site cannot be predicted, for example it may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The CTLs and cytokines may not adequately reach the target because of their inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the CTLs and cytokine have no effect, and circulation into the target area may be insufficient to carry the CTLs and cytokines, and a large enough local concentration may not be established. Thus in vivo killing of primary malignant cells by specific T cells cannot be compared to in vitro killing of cancer cell lines expressing Her-2/Neu.

Concerning Applicant's assertion that the Examiner fails to provide evidence that autochthonous immune response does occur, or that the response occurs in all individuals and tumors, it is noted since it is well known that the expression of Her-2/neu could be down-regulated in cancer cells, as taught by Cheever et al, one cannot predict whether the malignant cells in the claimed invention would not have down regulation of Her-2/neu expression on the cell surface. Thus one cannot predict that primary malignant cells would have adequate numbers of Her-2/neu on cell surface, necessary for malignant cell recognition and killing by T cells.

Further, concerning Applicant's assertion that the invention is not directed to cells that do not express a Her-2/Neu protein, it is noted that due to antigen downregulation, as taught by Cheever et al, of record, or due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, of record, one cannot predict that the targeted malignant cells in the claimed invention would have sufficient numbers of Her-2/neu molecules on cancer cells surface in patients, necessary for recognition and killing by T cells.

In view of the above, one cannot predict that the claimed method would be successful in killing malignant cells in vivo in cancer patients that express Her-2/neu as self antigen.

4) The amount of direction provided by the Inventor

Applicant argues that the specification discloses how to make the polypeptide of SEQ ID NO:10, and how to immunize animals with said polypeptide. Applicant argues

that the specification discloses that CTLs are activated by immunization, and that the collected activated CTLs target malignant cells that express a Her-2/neu protein in vitro.

This is deemed not to be persuasive. The specification discloses activating cytotoxic T lymphocytes in transgenic mouse that is cancer free, and that does not express Her-2/Neu as self antigen in normal tissues. The specification further discloses that said cytotoxic T lymphocytes could kill cancer cells line expressing Her-2/Neu in vitro.

The example provided by the specification cannot be correlated with successful production of specific T cells in patients with cancer burden, and having Her-2/neu as self antigen, wherein said T cells could successfully kill malignant cells in said patients, for reasons set forth above.

The specification provides insufficient guidance with regard to the issues discussed above and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

5-6) The Existence of working examples and the Quantity of experimentation needed..

Applicant argues that MPEP 2164.02 teaches that in vitro or in vivo animal model example constitutes a working example if that example "correlates" with a disclosed or claimed method, and further teach that there is no requirement of a working example. Applicant argues that the use of tumor cell lines was an accepted model

system for testing anti-cancer agents commonly used by the National Cancer Institute, as shown in *In re Brana*.

Applicant argues the experimentation needed to immunize an animal having malignant cells that express a Her-2/neu protein with SEQ ID NO:10 does not even rise to the level of being complex,in view of the teaching in the specification.

The recitation of MPEP 2164.02 and *In re Brana* is acknowledged.

The arguments are deemed not to be persuasive.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Thus, although an example is not always required, however, given 1) the unpredictability of killing target malignant cells by T cells specific for SEQ ID NO:10 in patients with cancer burden and having Her-2/neu as self antigen, for reasons set forth above, 2) the lack of correlation between production of specific T cells in transgenic

mouse that is cancer free and does not express Her-2/neu as self antigen and the production of T cells that could kill target cancer cells in patients having cancer burden and having Her-2/neu as self antigen, for reasons set forth above, and 3) the lack of correlation between killing cancer cells in vitro and killing primary cancer cells in vivo, for reasons set forth above, and in addition, 4) the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

1. Claims 64-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for specifically activating cytotoxic T lymphocytes in vivo in xenogenic transgenic mice without cancer burden, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vitro, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating the sequence consisting of tripalmitoyl-S-glycerycysteinyl-seryl-serine, does not reasonably provide enablement for a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating a second component, wherein said second component primes said CTLs for activation, and

wherein said second component comprises tripalmitoyl-S-glycerycysteinyl-seryl-serine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 64-67 are drawn to a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating "a second component, wherein said second component primes said CTLs for activation" (claims 64, 66). The second component "comprises" tripalmitoyl-S-glycerycysteinyl-seryl-serine (claims 65, 67).

The specification discloses that lipids have been identified that are capable of priming CTL in vivo against viral antigens, e.g. tripalmitoyl-S-glycerycysteinyl-seryl-serine (p.46, third paragraph).

It is noted that "a second component, wherein said second component primes said CTLs for activation" of claims 64, 66 encompass any component with any structure, provided it primes CTLs for activation.

It is further noted that due the language "comprises", the second component "comprises" tripalmitoyl-S-glycerycysteinyl-seryl-serine of claims 65, 67 encompasses any compound with unknown structure attached to the sequence consisting of tripalmitoyl-S-glycerycysteinyl-seryl-serine.

One cannot extrapolate the teaching in the specification to the scope of the claims. Applicant has not taught how to make the claimed numerous component, wherein said second component primes said CTLs for activation, or numerous unknown sequences attached to tripalmitoyl-S-glycerycysteinyl-seryl-serine. For example, Applicant has not taught what the structure is for the numerous component that primes CTLs for activation or what the structure is for the sequences attached to tripalmitoyl-S-glycerycysteinyl-seryl-serine.

Although the sequence consisting of tripalmitoyl-S-glycerycysteinyl-seryl-serine could bind to and activates CTLs, it is unpredictable that any lipids, or any compounds, or any sequences attached to tripalmitoyl-S-glycerycysteinyl-seryl-serine, the structure of which is not known, would have the ability to bind to and activates CTLs.
It is well known in the art that a specific binding of a ligand to a substrate requires specific interaction between the ligand and the substrate, and correct conformation of the ligand to fit into the binding site of the substrate, e.g. specific binding between a ligand and a receptor, or between an antigen and an antibody. Thus one cannot predict that any lipids, or any compounds, or any sequences attached to tripalmitoyl-S-glycerycysteinyl-seryl-serine would have the necessary conformation for specifically binding to and activating CTLs.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. Claims 68-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for specifically activating cytotoxic T

lymphocytes in vivo in xenogenic transgenic mice without cancer burden, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vitro, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating the peptide consisting of SEQ ID NO:9, does not reasonably provide enablement for a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating a second polypeptide, wherein said second polypeptide comprises SEQ ID NO:9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 68-71 are drawn to a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10, and further comprising administrating a second polypeptide (claims 68, 70). The second polypeptide "comprises" SEQ ID NO:9 (claims 69, 71).

The specification discloses that transgenic mice are immunized with p53-specific and HBc-specific peptides. The specification discloses that the HBc-specific peptide of SEQ ID NO:9, derived from Hepatitis B virus core protein, has been found to induce a CD4 T cell helper response (p.79, third paragaraph).

It is noted that "a second polypeptide" of claims 68, 70 encompass any polypeptide with any structure, for inducing a CD4 T cell helper response, as contemplated in the specification..

It is further noted that due the language "comprises", the second polypeptide "comprises" SEQ ID NO:9 of claims 69, 71 encompasses any compound with unknown structure attached to the sequence consisting of SEQ ID NO:9.

One cannot extrapolate the teaching in the specification to the scope of the claims. Applicant has not taught how to make the claimed numerous polypeptide for inducing CD4 T cell helper, as contemplated, or numerous unknown sequences attached to SEQ ID NO:9. For example, Applicant has not taught what the structure is for the numerous polypeptides for inducing CD4 T cell helper, as contemplated,or what the structure is for the sequences attached to SEQ ID NO:9.

Although the sequence consisting of SEQ ID NO:9 could bind to MHC molecule and induce a CD4 T cell helper, it is unpredictable that any polypeptide, or any sequences attached to SEQ ID NO:9, the structure of which is not known, would have the ability to bind to MHC molecule and induce a CD4 T cell helper.

It is well known in the art that a specific binding of a ligand to a substrate requires specific interaction between the ligand and the substrate, and correct conformation of the ligand to fit into the binding site of the substrate, e.g. specific binding between a ligand and a receptor, or between an antigen and an antibody. Thus one cannot predict that any polypeptide, or any sequences attached to SEQ ID NO:9

would have the necessary conformation or would be correctly processed for specifically binding to MHC molecule and induce a CD4 T cell helper.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102 (b or e), NEW REJECTION

1. Claim 1 is rejected under 35 USC 102(b) as being anticipated by Grey et al, of record.

Claim 1 is drawn to a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10.

Claim 1 reads on a method for specifically activating cytotoxic T lymphocytes in vivo in mice without tumor burden.

Grey et al teach injection into transgenic mice putative CTL epitopes for inducing specific CTLs, and testing for lysis of peptide-coated target cell line Jurkat that expresses the A2 KB molecules (p. 76 and table 24). Grey et al also teach identification of immunogenic peptides, wherein one of the identified peptide is VMAGVGSPYV (p. 108, sixth sequence) which is from c-ERB2 (or Her-2/Neu), and has A2 binding affinity of 0.018 and which is exactly the same as the claimed SEQ ID NO:10 (Example 12 on page 79 and page 108, sixth sequence). Grey et al further teach that based the results

on table 24, peptides that have a binding of at least 0.01 are capable of inducing CTLs (page 76, last paragraph).

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

2. Claims 1, 68, 70 are rejected under 35 USC 102(e) as being anticipated by Cheever et all, of record.

Claim 1 is drawn to a method for specifically activating cytotoxic T lymphocytes in vivo, wherein said cytotoxic T lymphocytes specifically target malignant cells that expresses a Her-2/Neu protein in vivo, the method comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:10.

Claims 68, 70 are drawn to the method of claim 1, further comprising administering or co-administering a second polypeptide to said animal .

Cheever et al teach peptides from p185 Her-Neu protein suitable for CD8+ T cell response, which include SEQ ID NO:27 (column 11, lines 23-30). SEQ ID NO:27 is exactly the same as the claimed SEQ ID NO:10.

Cheever et al further teach immunization of an individual with a Her-2/neu peptide (i.e. as a vaccine), which can induce continued expansion in the number of T cells necessary for therapeutic attack against a tumor in which the Her-2/neu oncogene is associated (column 13, last paragragraph, bridging column 14).

Cheever et al also teach in addition to the Her-2/neu peptide, which functions as an antigen, other components, such as immunostimulatory substances, IL-12, GM-CSF, gamma interferon and IL-15, may be included in the vaccine (column 14, second paragraph).

Because the method of the prior art comprises the same method steps as claimed in the instant invention using the same composition, the claimed method is anticipated because the method will inherently lead to the claimed effects. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PHD
PRIMARY EXAMINER

MINH TAM DAVIS

August 13, 2004